Essays on Tuberculosis

XXII REINFECTION

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XXII. Reinfection

By ALLEN K. KRAUSE, M.D.

IT is plain that the *opportunities* for tuberculous infection are extraordinarily frequent throughout life. Every phthisical associate, at home, in the workshop, or in the office is a potential source of infection. All objects, furniture, floors, highways, articles of everyday use and traffic, food, contaminated by the sputum of consumptives, can originate tuberculosis. All sputum-contaminated dust and dirt, in which bacilli remain alive, are also infectious. Many cows eliminate bovine bacilli in their milk, which is then used for food.

The vigorous campaign of education which for years has been gaining in momentum and effect, the training obtained by a growing number of patients at sanatoria, and the instruction which school children receive have done much to lessen the indifference of both patients and contacts to the possibilities of infection. The increasing use of pasteurized milk has improved the bovine tuberculosis situation as it touches human beings. But, viewing civilized humanity and its activities as a whole, one cannot help concluding that there are still at large enough tubercle bacili "to go around"—enough, and a great many more.

Sanatoria and other institutions are, as yet, training only a fraction of consumptives. The majority of people are yet to be educated, at least to the point where they will carefully guard their own sputum or themselves from that of others. Most children bother little about dirt or germs, when the impulse to play is upon them. The milk that is pasteurized is little more than a drop in the bucket.

Opportunities for Infection

There are still thousands of homes with mother, father, or both phthisical, cramped and pinched by the poverty that is one of consumption's most grisly followers, where children live and play continuously for long periods in a thoroughly contaminated environment. Into their nostrils, into their mouths and onto their persons must go virulent tubercle bacilli every day and many times a day.

There are infants and children who for weeks and months are ingesting tuberculous milk; and not a few adults are having the same experience.

There are husbands and wives living in most intimate physical contact with consumptive consorts whose habits leave much to be desired from the point of view of care and cleanliness. Most of us, at some time or other, must have been coughed or sneezed upon by a consumptive. All of us have had the sputum of others on our hands, whether it got there from the handling of our own shoes or of other objects about us which were contaminated by sputum tracked into the home or of articles soiled directly by consumptives themselves.

I have known a street car conductor, so far gone with pulmonary and laryngeal tuberculosis that he could hardly stand up to his work, who for over a year after diagnosis continued to make change and hand out transfers to the thousands who passed his fare box. My observation of the thumb-licking which is part of the average conductor's "business" in tearing off transfers excited my fancy to somewhat grandiose ideas of this man's range of infection.

A few months ago I examine an octoroon who has active pulmonary tuberculosis with cavity and a warty, verrucous tuberculosis of his left thumb. His occupation has been that of "following the race tracks," in the capacity of waiter and dishwasher (!) in restaurants which serve thousands.

I once knew a prominent pediatrician, who for eleven years before diagnosis had active pulmonary tuberculosis. At diagnosis he was a far advanced case. What, during all these years, was his contact with children and the character of it, one can only guess.

I have met with a child playing with a thermometer case which had been given to him by a consumptive, "taking the cure" under the best conditions and medical supervision. When I saw the child the case was in his mouth. A few months later this child gave a violently positive Pirquet reaction: on two separate occasions before the incident his reaction had been negative. Was the child infected by the case? I don't know. But had he not been accidentally discovered with the case, the source of his infection would have been a thorough mystery. It may smack of the ironic to insist that the owner was a "trained" consumptive.

A very eminent phthisiologist, whom I knew and who had tuberculosis, was now and again wont to upset his neighbors quite a little by clearing his throat and spitting on his lawn.

Not long ago I sat opposite a well-known student of tuberculosis. At the time he had a hard and very explosive cough. During the conversation he coughed directly toward me at least a score of times without once attempting to cover his mouth.

So much for opportunities of infection. I cite the above incidents to point out the wide gaps that exist between education and performance and to show how unconsciously we may come in contact with tuberculosis. My own experience cannot be unique. It leads me to believe that we receive tubercle bacilli much more frequently than we can be aware of.

Again, when we speak of training consumptives to take care of their sputum, we must remember that a great many develop active pulmonary tuberculosis some time before they find out the nature of their disease. And it is certainly true that most of us begin to exercise reasonable care only after diagnosis has startled us into more cleanly habits.

The Data of Infection

Our analysis of the data of infection led us to conclude that tuberculous infection of human beings occurs through several avenues and in a variety of ways. Anything carrying living tubercle bacilli and capable of being introduced into the mouth, or of being inhaled or injected, can set up infection. Not all germs which are taken into the body need initiate lesion. Many may be undoubtedly spat out or passed on through the faeces. We cannot admit that the deep inhalation of dust and droplets is responsible for almost all infections, though we cannot disprove it to a certainty. We believe that "hand to mouth" infection is a much more common method than has been generally assumed.

We found also that infection—primary infection—usually takes place before adolescence is completed: this simply means that the tubercle bacillus is so ubiquitous that by the time the ordinary activities and experiences of childhood are completed most of us will encounter it somehow and somewhere. We noted that when symptomatic disease occurs, it manifests itself in children most frequently in the lymph nodes, especially those of the neck, which are in direct communication with the two major portals of entry. In adults, however, pulmonary tuberculosis is far and away the most prevalent type of disease. Moreover, when pulmonary disease does take place in children, as very often happens, it does not usually begin in the same part of the lungs as in adults. In the latter, early pulmonary disease is more prone to appear in the peripheral or marginal parts of the lung, especially near the summit (apex): in children, it is at the root or *hilum* of the lung where we are accustomed to find the first evidences of pulmonary tuberculosis.

Such, in broader outline, are the relatively undisputed features of tuberculous infection, which we must keep before us as we plunge deeper and take up the matter of reinfection. Summed up, they prove that most children receive an infection before adolescence, they suggest that tubercle bacilli localize at first most frequently and in greater profusion at the surface of the body near a portal of entry, and they indicate that when infection does reach the lung in early life it tends to accumulate first at the root, while in adult life it finds conditions further out in the lung more favorable for its development.

Chances of Reinfection

Until recently it was generally believed that the number of infections which anyone received from without was limited only by one's opportunities for infection, and that repeated infection represented one's average experience. But within the last few years this presumption has been seriously weakened by our recognition of immunity and our discovery that most people are infected early in life.

Since immunity results from infection and since most of us are infected, then most of us are immune to reinfection: this was the form of the argument which, from frequent repetition, took on a more and more positive tone.

In some quarters it has hardened into a doctrine which teaches that, once infected with tubercle, a person can never again become infected, except under unusual circumstances. The logical consequences of such a belief are that the average human experience is to sustain *a single and isolated infection from without* and that, after this is acquired, subsequent contact with tubercle bacilli is ordinarily harmless. If, as tests prove, an infection is received by most children, then this is the only infection which these positive reactors will, as a rule, undergo. If, therefore, tuberculous disease (usually pulmonary) breaks out in later adult life, it is but a development of early childhood infection. And, guided by the fact that three-fourths and more of our children exhibit infection, some would go so far as to maintain that *all adult tuberculosis comes from infection established in childhood*:—the exceptions which these men cite are so few relatively, that they only confirm the generalization.

This opinion, which has gained a wide, though by no means general acceptance, is by far the most important development of our point of view in a half century—since the demonstration of the infectiousnes of phthisis. It has not the definite and clean background of proof that is available to anyone who would test infectiousness. But it does have much to commend it. It collates and brings into relation well-determined data from several widely divergent sources, the phenomenon of immunity, laid bare by animal experimentation, the fact of "universal" infection revealed by epidemiological studies, and the circumstance of the extraordinary durability of tuberculous lesion long known to pathologists and clinicians: and by induction infers from these the conclusions above set forth.

These conclusions, therefore, are more or less valid according as the premises upon which they are based are more or less sound. Without for the present committing ourselves to whether a positive skin test inevitably discloses a first or repeated infection, we may grant that the case for general childhood infection is established beyond a doubt. If, then, immunity because of it persists throughout life and if it protects to the point of *preventing* reinfection and if *all* tuberculous lesions, containing living tubercle bacilli, are permanent, the conditions are established which compel our acceptance of the non-reinfection doctrine. In discussing reinfection, therefore, our task is to subject these premises to rigid analysis.

Tuberculous changes *may* continue in tissues with a tenacity which is almost unique for pathological formations. In some people who have been under observation because of an active tuberculosis from which they have recovered we find that the original site of the disease remains affected for many years. Patients may relapse after intervals of good health of as long as thirty or forty years after a former illness and show the second attack of active disease in the spot where the first was located. In these patients it is beyond question that relapse is due to renewed activity of old foci, and that during the interval of good health the infection had merely been in abeyance. I recently saw a girl of fourteen with fresh tuberculosis in the scar of a neck wound which resulted from an old tuberculosis of the lymph nodes appearing when the girl was a year old and becoming inactive and healed by the time she was three. I have no doubt that this second attack is a renewal of an old infection which was not eradicated. I have in mind a young man who when an infant played on the floor of a room in which his consumptive grandmother was bedridden. At three or four years of age he developed tuberculosis of the lymph nodes of the neck; at fourteen he was found to have a tuberculous kidney which was removed; and shortly after passing twenty he was stricken with active pulmonary disease which proved fatal. His cervical and kidney tuberculosis were each recovered from, and he had periods of average health between his several attacks. It can hardly be denied, however, that his three illnesses from tuberculosis of widely separated organs were all but several episodes in the course of one and the same infection.

Living Bacilli in the Body

We also have some evidence that even though infection is inactive living bacilli may persist in the body under surprising conditions. One of the effects of tuberculous infection is the death and destruction of tissue. Sometimes, when such necrotic areas heal, lime salts are deposited in them and take the place of the dead cells. This process is called healing by *calcification*, and is looked upon as the most satisfactory and permanent form of healing. Yet living, virulent tubercle bacilli have been found in these stony masses.

The wider one's clinical experience, the more extensive one's practice with tuberculous patients, the more accurately and minutely one goes into the past history of these patients, the more will one be impressed with the certainty that first attacks of active pulmonary tuberculosis are in very many people the culmination of a long antecedent infection. It is rarely given us to say with complete confidence that a particular outbreak has resulted from an infection of which we can have some idea of the localization of the bacilli. Yet I may cite a case which will illustrate how slowly it may take particular infections to exhibit their effects.

A boy, not quite four years of age, fell ill with tuberculosis of the lower part of the forearm. This focus was operated upon and the wound healed. A year later he began to show manifest tuberculosis of the lymph nodes of the elbow, which drain the region of the forearm and are only a few inches away. This slowly subsided, so that after another year the nodes were apparently normal. Five years after his bone tuberculosis, four years after the first signs of tuberculosis in his elbow nodes and three years after these had returned to normal, he developed tuberculosis in the lymph nodes of the armpit, the chain which stands next to those of the elbow. This progressed to a point which made surgical operation necessary.

Here we have a child with manifest tuberculosis appearing at proximate and related points only after an interval of years and after the former disease had disappeared. We have no other way than to assume that infection of particular regions long antedated its manifestation. During all this time, the boy was under observation once or twice weekly, so that there can be no question of the course of events.

Is Infection Permanent?

But to be convinced and to be able to demonstrate that bacilli and infection frequently persist extraordinarily long in the body and that many cases of active disease at all ages arise from long-persisting infection is far from proving that all conceivable types of infection are of a permanent nature or that all or most active tuberculosis is the consequence of first infections. In fact, there is good evidence to the contrary.

Whoever has a sufficient acquaintance with experimental tuberculosis and the performance of human autopsies and surgical operations will agree that tuberculous foci can disappear completely and can also heal by scar formation so completely as to be entirely free from bacilli.

Not a few surgeons have performed successive operations on the same patient which disclosed the replacement of tubercles by normal tissue. A first operation would show multiple foci studding, say, the peritoneum; a second, some time later, would bring to light a perfectly normal peritoneum, with all traces of tuberculosis gone.

Before we knew of the Pirquet test as an index of infection, Naegeli, on the basis of autopsy findings, startled the world with the declaration that almost all human beings, past twenty-one years of age, would show tuberculous infection or its remains. "Its remains" characterized a large proportion of the cases upon which he based his opinion. "Its remains" frequently meant scars in the pleura at or near the lung apex, which not all pathologists would grant represented the former location of tuberculous infection, However, in the absence of proof to the contrary, such scars are generally accepted as being the results of healed infection. If they are, then in nearly all of them the bacilli have died out and we have complete healing; for usually they are found to be without tubercle bacilli. Although, as mentioned above, living bacilli have been found in calcareous nodules, they are not always there. What little we know indicates that most of such healed areas would prove to be sterile.

It is, however, in controlled experiments on animals that I have often observed the most striking instances of the complete obliteration of tubercles. If rabbits are given comparatively large inoculations of *human* tubercle bacilli and the results of inoculation are studied from time to time over a long period, it will be found that while those animals of the experiment, which are killed from two to five and six weeks after inoculation, will show numerous tubercles in their lungs, survivors, six months and more later, have few tubercles or none. Again, if a large series of immunized rabbits is infected with virulent tubercle bacilli, those which are killed and examined several weeks after infection will have lungs which are very extensively involved, while those allowed to live for six to twelve months will at the end of this time have only scattered tubercles, with intervening normal lung tissue or wholly normal lungs.

Such experiments prove that tubercle, whether in normal or immune animals, may clear up completely, and raise the presumption that the same process goes on in human beings. If foci which result from extension of infection from older lesions can heal completely, it assuredly follows that first or original foci can similarly disappear. Older points of infection are by no means necessarily more extensive, more active or more serious than younger ones. Kidney or bone or meningeal disease is often the *primary* manifestation of tuberculosis. Every case of one of these types must have originated from older foci in the body: yet it is very common to meet with patients afflicted with kidney, bone or meningeal tuberculosis, in whom the primary *infection* is so slight as to have escaped notice and to be impossible of detection during life. Years ago I performed an autopsy on a child who had died of tuberculous meningitis, and in whom the only other detectable tuberculosis was a small calcareous nodule in a lung.

Is Reinfection Possible?

The non-reinfection idea has, however, derived most of its plausibility and vogue from the demonstration that immunity to tuberculosis exists. Increasing application of this knowledge has kept step with our widening acquaintance with it:—to an extent, indeed, that one must ask whether many writers on the subject are thoroughly familiar with the qualifying details of the phenomenon. The text-book of one author who adopts the non-reinfection point of view states in substance in its preface (I do not have the volume before me) that it has been shown that a tuberculous animal cannot be reinfected: it is therefore implied that tuberculous human beings can never again be infected. Others found their belief on premises which must assume that, with few exceptions, human beings are infected once—and only once; and that this original infection establishes a permanent and fixed immunity which is sufficient to resist all future contacts with living bacilli. The only exceptions which they will usually allow are the results of receiving what they are pleased to call "massive" infections, as a sequel to which they teach that clinical disease ensues: most cases of disease, however, they view as the extension or development of first infection. They must admit with everyone else that while most of us are infected, relatively very few of us fall ill with tuberculosis: they admit also the extraordinarily frequent opportunities for infection: they minimize the importance of these opportunities in the scheme of infection, because they believe that our first infections render all subsequent contacts harmless: they explain the failure of most people to develop clinical tuberculosis on the basis of specific immunity acquired from first infection which protects against outside infections otherwise capable of producing manifest disease as well as against the further advance of whatever tubercle may be present in the body.

Few, if any, of the elements which make up the accurate and scientific part of our concept of immunity to tuberculosis have been derived from clinical observation of human beings: practically all of them have come from studies of animals under the conditions of controlled experiment. It is questionable whether anyone, familiar at first hand with the effects of experimental infection, would have the hardihood to state

that the tuberculous animal cannot be reinfected.

Trudeau certainly did not find this to be true; neither did Koch; nor Roemer; nor Hamburger; nor any other first class observer. *The tuberculous animal can always be reinfected.* What is more to the point, the tuberculosis animal of experiment usually is reinfected. Experiment will show that in the tuberculous animal, a second or later infection will not proceed the same as a first infection; nevertheless second and later inoculations of living tubercle bacilli will produce results which are infection and lesion none the less. If immunity at the time of reinfection is sufficient to cope with dosage of bacilli, the result is *modified infection and modified lesion.* Infection may be unusually well localized, that is, it may not spread far from the point of inoculation. Yet it is the rule for living, virulent bacilli and lesion to persist for a long time; for months and even years in guinea pigs and often giving rise to pathological changes which, if present in human beings, would certainly make for active, clinical tuberculosis.

Infection and Activity.

It is not in a failure to become infected that the tuberculous animal commands attention. What is impressive is the altered character and course of the resulting lesion which an actually reinfected animal exhibits. What is suggestive is that these resemble so closely the character and course of tuberculosis as it is *most commonly* observed in sick human beings, except in very young infants. In by far the greater number of such human beings the tendency of lesion is towards arrest—at least, toward temporary arrest.

In basing our view of human tuberculosis upon observations made on animals, we must be very careful to bear in mind that effects may be considered exactly comparable only when underlying conditions can be shown to be exactly similar. This commonplace may be allowed here, because the following fact is usually neglected in the reckoning; namely, that the known conditions of experimental infection of lower animals usually bear no conceivable resemblance to those of natural human infection.

Infection and immunity experiments have been performed on many animals. Of these, guinea pigs and rabbits become spontaneously infected (under natural conditions) only with extreme rarity. Among cattle spontaneous tuberculosis is a plague. Sheep are practically never found with tuberculosis. Dogs, through assocation with human beings, are probably more frequently infected than we assume. From recent studies it would seem that the same thing is true for goats. Of all these animals, dogs, goats and sheep have proved to be most resistant to experimental infection.

In order to be able to interpret results correctly, we are careful to begin experiments on healthy, non-tuberculous animals. In the case of cattle which are so prone to natural infection, this involves taking them out of a tuberculous environment and keeping their environment closely guarded. We must have conditions so well under control that we know to a certainty exactly how, when, and how severely every animal is infected.

Infections, however, whether first or later ones, are usually brought about by introducing with a needle large numbers of bacilli at one spot. Unless resistance to natural infection is being studied, the animals are not allowed to live under conditions which would make possible continuous or repeated opportunities for infection. If repeated infections are made, these are given at definitely spaced intervals, at times when the animals are known to possess a high immunity. The animals, meanwhile, are scrupulously protected from outside debilitating influences: if any fall ill with diseases other than tuberculosis they are usually withdrawn from the experiment.

It is only by such rigid control of our animals that, by excluding every possible external effect, we can hope to obtain accurate information about the one thing we seek to learn, namely, the immunizing results of infection. Our long survey of immunity taught us that such methods of study revealed almost unerringly that infection, in and through itself and with no reference to other factors, brings about a relative, incomplete and fluctuating immunity, which is subject to modification by a number of both specific and non-specific influences.

In considering first human infection, we have no other way than to assume that it takes place under every conceivable condition of numbers and virulence and primary localization of bacilli and of good or impaired health of the recipient. Every one of these factors would potentially exercise its influence on the character of the first focus in any given case: and, while the conditions of experiment may be varied in animals so as to produce variable effects, the possible number of diverse effects obtainable in them will bear no comparison with what must all the time result from natural human infection.

Immunity to Reinfection

Nevertheless, they furnish us with standards: for we have seen that the effectiveness of specific immunity to reinfection varies directly with the vigor and activity of the lesion; that, unless it be renewed by reinfection, immunity tends to die out; and that immunity is markedly influenced (lowered) by such incidents as other diseases (infection), fever, pregnancy, etc. We must presume—and are no doubt correct in doing so—that first lesions in human beings vary from the slightest and most transient ana-

tomic formations to those that are permanent and spreading. It must frequently happen that the first intake of bacilli represents only a few germs. Perhaps only one is concerned. If bacilli be arrested superficially and if native tissue reaction is good, the primary lesion under such circumstances might conceivably be an accumulation of only a very few cells, hardly enough to be even microscopically demonstrable upon routine examination. Bacilli have not infrequently been proved by inoculation to be present in tissues, after careful gross and microscopic examination had pronounced the latter to be without tubercle.

We would expect many of these slighter infections to be so well taken care of that they disappear. Who knows but that most first infections result from the reception of very few bacilli and that most first infections disappear? In view of the fact that it is only the comparative few who are in close and continuous contact with consumptives and that tuberculization of the race rapidly becomes well-nigh general, it is certainly as plausible that most first infections are slight as that first contacts are mainly with larger numbers of bacilli.

Again, as we have said, we incline to the view that average human experience would show relatively frequent and repeated contacts with living bacilli. The spacing of contacts would be subject to every variation. For some the interval would presumably be months or even years. For many it would undoubtedly be days or weeks. For those in not a few phthisical homes it must be so close and persistent as to merit the term, continuous. To simplify our analysis, let us suppose (what is not true) that, although in all cases the spacing varied, the infecting doses remained the same, say, moderate or slight. We cannot believe that even then the results would be the same; that those who had two contacts with living bacilli months or weeks apart would react to second or later infections, would have the same immunity at all times, as those who received bacilli frequently at long intervals.

Animal experimentation teaches us that, altogether apart from such factors as dosages of reinfecting bacilli, we must expect to find in human beings every degree of immunity, every variety of lesion, or even no lesion, at proper intervals after some first infections. It compels us to believe that in many immunity is being lost by the total cure of slight lesion; that in others it is being fortified by the reception of new bacilli, which we cannot conceive of as being always (unless dosage is large) only an affair of the nesting and destruction of bacilli without pathological change; that in still others it is being reduced by the gradual subsidence of underlying lesion or by outside influences.

Bacilli will be received by people in every condition stated above and the result is bound to be different. Some, once infected, but now free, will be specifically as non-immune as though they had never before come in contact with bacilli: they will have nothing but their native reacting capacity with which again to fend off reinfection. Some will undoubtedly resist their particular reinfection completely, others only partially.

Repeated Infections

It may be mentioned here also that we have very little detailed information about the effects of numerous infections from without, repeated at very short intervals. This phase of immunity has scarcely been touched in animal experimentation; yet it cannot be doubted that many human beings live in an environment which establishes these very conditions of infection. Children in dirty "tuberculous" homes or infants ingesting "tuberculous" milk over a long period would experience this type of infection.

Though the scientific evidence on this point is scanty, we would presume that frequently repeated intake of bacilli, at very short intervals between, would make for reduced immunity. I have reported experiments which showed that tissue allergy is greatly lowered or completely suppressed during a constitutional tuberculin reaction and for a short time afterward. I have also recorded how reinfection with virulent bacilli into skin areas of tuberculous animals, which were the sites of tuberculin skin reactions one or two days before, meet with less resistance than do reinfections into normal, non-reacting skins of immune animals which are similarly tuberculous.

Such experiments indicate that during the period when an artificially immunized animal is laboring under the local or constitutional effects of intoxication—in these cases, specific intoxication—its immunity is less than before. We have ample clinical evidence of this fact in patients who are overwhelmed and made profoundly ill by the intoxication of an acute tuberculosis: during this period they lose in allergy, which we can prove, and quite likely in immunity, which subsequent events not infrequently indicate.

Many investigators have pointed out that for a very short time after every act of reimmunization, after every successive reapplication of antigen, after every reinfection, animals show a sharp and transitory fall of immunity which is rapidly recovered from. There is every reason to believe that this same phenomenon occurs after every tuberculous reinfection.

If, however, reimmunization or reinfection is performed at too short intervals, the body has not the time to restore and increase its previous measure of immunity. The result is that it falls into a state of continuously lowered resistance.

In children who are continuously exposed

to living tubercle bacilli, we should expect this very thing to happen in many instances, and result in an increment and accretion of infection from without. What would actually happen in every given case would be the sum total and balancing of several factors:—separate dosages of bacilli and their relations to one another, points of the several focalizations, the time of reception of every single reinfection as related to the one before it and the state of immunity at the time, etc.

It is of the greatest significance that the testing of immunizing methods, by placing cattle under the conditions of ordinary natural infection, has always proved disappointing. The very men who maintained that they got favorable results, that their cattle resisted reinfection well, when they were tested by single spaced reinoculations after primary protective inoculation, acknowledged that many more developed progressive tuberculosis if, after immunization, they were placed in stables or herds known to be infected.

I am inclined to believe that immunization was of so little avail against natural infection, because in this case the cattle lived under conditions of continuous exposure, and repeated contact with tubercle bacilli set up the state of diminished resistance which we have just described. It is impossible to believe that separate natural infections were so large or "massive" as the really large ones which one is accustomed to introduce *in one spot and into the tissues underneath the surface* when one performs artificial reinfection. As the term is often and gratuitously used "massive infection," if meant to describe single, separate and isolated incidents in the natural life of man, has many of the elements of a figment of the imagination. It is the easiest thing in the world to perform massive infections artificially. It is as certain as anything that they frequently occur in human beings from parent foci already present, as, for instance, by the discharge of ulcerated lesions into veins or great lymphatic trunks. It is not so clear to me how they can occur under natural conditions (except by wounding) *from the outside*—how large numbers of bacilli reaching any point *on a surface,* whether mouth, throat, bronchial or intestinal mucous membrane, can swarm through and past the surface, at a point of entry into the tissues underneath, which must be their location before they can set up lesion (infection). Until I am shown otherwise, I am inclined to believe that frequently repeated infection at short intervals has a much more real and tangible existence than has "massive" infection.

Evidence of Reinfection

Strong evidence that reinfection from without cannot be so uncommon lies in the circumstance that the extension and spread of infection from parent foci to other points, which, of course, is nothing else than reinfection from within, is one of the characteristic features of the normal course of tuberculosis.

An adherent of the doctrine of non-reinfection from without might offer several explanations of this extraordinary phenomenon. He might, for instance, assert that the tuberculous, immune person stands in a different relation to bacilli from without than to those from within;—that, because of prolonged residence in the body, certain adaptations between bacilli and host have taken place, adaptations which would result in raising the parasitism of the bacilli for their particular host—to a point exceeding that of foreign germs newly received from without. This explanation would rest on a sheer speculation. There is no scientific evidence to support it: we possess, however, not a little information to the contrary.

Or one might maintain that all reinfections from within are "massive;" or rather more massive than those usually coming from without. Many from within are massive, very massive: we have said this much before. But to maintain that all reinfection from within, which "takes" and initiates new foci, must be massive is to stretch probability beyond belief.

We come across cases with tuberculosis at the top of the lung, where we can determine that the infection has existed for years. During all this time it slowly progressed, most likely haltingly, periodically, and in a sort of "ebb and flow" fashion. In its excessively sluggish advance new foci have arisen, some by short excursions—a millimetre or two—from older lesions. There may be several minute lesions, originating one from another, yet separate and discrete, and at a distance of a fraction of an inch from one another. We find few bacilli in the foci; sometimes it is hard to detect any by direct examination. There is nothing to suggest that bacilli in large numbers were ever present in the lung: there is everything to make us believe that reinfection from point to point was brought about by the repeated conveyance and focalization of very few bacilli.

Again, we may have before us a patient with kidney or joint disease. Involvement is extensive. We are sure that the kidney or joint infection originated from some other antecedent focus in the body. Yet the latter is so insignificant that it has never exhibited activity and cannot be detected during life. Autopsy has shown that in some cases like this it has been very slight: the case, mentioned above, of meningitis, with a small calcareous nodule in the lung the only other focus, may be recalled here.

These are not uncommon incidents in tuberculosis—this development of new foci from slight and quiescent (clinically inactive) parent lesions. If we consider tuberculosis in its broadest aspects and as a whole, they

represent perhaps what most frequently happens. They surely cast doubt on the idea that reinfection from within must require large numbers of bacilli. We repeat here that reinfection from within—from extensive or rapidly progressing lesion—is frequently "massive;" but we are now considering how tuberculosis develops for most in that long thoroughly silent period which lies between the reception of an infection from without and its growth through its own direct extension or procreation of generations of descendant foci to the point where clinical disease makes itself felt. Before accepting the idea we must ask for better evidence than has yet been put forward that reinfection from within is based on "massive" infection.

One might, of course, contend that reinfection from within by few bacilli takes place in immune persons at times when local and constitutional conditions are temporarily favorable for the focalization and persistence of the germs. During pregnancy or lactation, during and for a short time after measles or influenza, during periods of food deprivation or of long-continued fatigue, anaemia, etc., a few bacilli from other foci might presumably set up lesion in people for whom they would be harmless in times of perfect health. But such an explanation is simply begging the question. Pregnancy, other infectious diseases, semi-starvation, etc., are all incidents of ordinary human experience. And if reinfection from within is more likely to occur—in other words, if resistance to one's own infection is lowered—then, why do we not also strike the same relations with bacilli from without? The answer is that we very likely do.

Deductions from Animal Experiments

It is in this very respect that in considering human immunity and infection we dare not adhere too rigidly to norms and standards which have been derived from observations on animals of experiment. Much that we note about tuberculosis is obscure, but nothing about it is clearer than that in almost every phase it is profoundly affected by environmental influences and delicately responds to these. As we said above, infected and immune animals of experiment are made to live in a carefully regulated environment, so adjusted as to remove anything that may modify the infection. When the experiment is extended to immune cattle which are permitted to live their normal life—to become pregnant, to be exposed to the vicissitudes of weather, of stabling, of diet, etc.,—results are different. When, accordingly, we reflect on the enormously different and variable conditions in which human beings live and move, and which therefore must alter, almost infinitely, their relations with natural infection, we can only plead for more study, more desire for understanding of a problem of extreme intricacy, and less offhand and hasty, rigid generalization. Let us repeat: animal experimentation teaches us the how, the why and the when; before carrying these over to human beings in a positive way, let us make sure that they fit in with human experience.

And experiment has given us accurate data which if used rightly does fit in with human experience and explain, in part, human tuberculosis—but quite differently than "once infected, always infected," or "a person, who has been infected cannot again be infected, except by massive doses," or that "all adult tuberculosis develops from childhood infection." The trouble is that the data have been misused, neglected in detail, or only partially understood and applied.

Summary of Immunity and Infection

Let us once more run rapidly over what experiment has taught us concerning immunity and infection.

1. Infection with living tubercle bacilli endows its recipient with increased resistance, with immunity.

2. At its best, this immunity is incomplete.

3. At its best, it expresses itself, not so much in warding off infection with a total non-appearance of lesion, as in a modification of the resulting lesion.

4. It is at its highest as lesion develops and progresses.

5. It diminishes as lesion subsides and heals. If guinea pigs are immunized with human bacilli of low virulence, which do not produce fatal infection, then with the lapse of time, as lesion becomes more and more scarred in, immunity declines. If cattle are immunized by single inoculations of living human bacilli (of comparatively low virulence for them) immunity becomes reduced to a non-effective point in from one to two years,—as first infection becomes well walled off.

6. A falling immunity is rapidly restored and raised by reinfection—*after the immediate depressing effects of the reinfection wear off*.

7. An immunity of any degree may be adversely influenced by many environmental factors.

8. Though the end result of reinfection is to raise immunity, repeated reinfections, too closely spaced, greatly depress resistance.

It is fair to assume that all these features of immunity are at work in human beings. After analysis of the relations which human beings establish with tubercle bacilli, we are led to believe that:

1. The opportunities for repeated infection are presented to everyone.

2. These opportunities are of infinitely varied degree and manner.

3. In bringing about first infection, they

will result in every type of lesion from the slightest to the most extensive.

4. Infections and lesions can heal without leaving a trace. Lesions can heal by scar formation with the eradication of bacilli (sterilization).

5. Reinfection from within is a common event in human beings.

6. Reinfection from within need not require the new focalization of massive doses from parent foci.

7. The immunity, acquired by human beings because of infection, is continually fluctuating.

8. Some, presumably, have slight infections completely eradicated between successive exposures. These would lose all immunity acquired from the earlier contact and be as open to later infection as a person who had never been infected.

9. In others the first infection or foci descendant from it may persist. In them a measure of immunity would coincidently continue.

10. They may, however, be open to reinfection from without at times when their immunity were lowered by any one of a variety of experiences.

11. When immunity exists, reinfection is probably contingent not so much on single "massive" infections as on repeated infections suffered at too close intervals.

12. Active descendant foci arise from quiescent parent foci. Therefore, active foci from reinfection from without may occur in those with quiescent foci from earlier infection already present in the body.

13. The bare fact that there is an immunity to tuberculosis has been greatly overplayed in our interpretation of the natural development of tuberculosis in human beings.

A Fallacy

There is much more that might be said about reinfection and human tuberculosis. At this time, however, we would limit our analysis to reinfection, considered purely by itself, and reserve further comment on it until we come to take up the etloiogy of tuberculosis. But in closing, it may be apropos to point out what without injustice may be considered to be a curiously fallacious association of concepts in the minds of some writers.

There are some who entertain the following two opinions: first, that practically all adult (pulmonary) tuberculosis develops from childhood infection; and second, that adult pulmonary tuberculosis is the result of infection inhaled deep into the lungs where it develops.

Now, there is no doubt that most adult tuberculosis (clinically) is pulmonary. There is also no doubt that most first infections take place in childhood. If, then, most adult tuberculosis developed from childhood infection, it should be an outgrowth of tuberculosis where it is found most commonly in children. This place is the lymph nodes of the neck. Therefore, we would assume, that most adult tuberculosis arising from childhood infection, would represent spread of infection from the lymph nodes of the neck to the lungs. Therefore, the lung foci of these adults are not the result of bacilli breathed deep into the lung from the outside.

If neck node infection, suffered in childhood, makes its possessors always permanently and completely immune, most human beings cannot later suffer direct lung infection from without—for they would resist it.

As a matter of fact, most pulmonary tuberculosis in children appears, as before mentioned, in a very different part of the lung than does adult pulmonary tuberculosis. It usually begins at the root of the lung: adult tuberculosis, at the top. If apical adult tuberculosis is the end result of childhood root infection, it is curious that traces of extension by continunity are lost in nearly every instance; for surely in our thousands of cases, we should record a fair number of instances—if this were the common history. But we do not.

The facts of the case cannot fit both of the two hypotheses of (1) almost universal development of adult tuberculosis on childhood infection and (2) almost universal infection by pulmonary inhalation. If twisted to fit hypotheses, they make it appear: (1) either that pulmonary tuberculosis in adults comes from primary neck infection, that is, if immunity is fixed and always competent; or (2) that immunity does not prevent reinfection from without, that is, if pulmonary tuberculosis is a deep inhalation infection.

As is usual, when opinions, founded each of them on a considerable body of observation, clash so squarely, it is probable that the truth lies between:—that as regards this dilemma, many people are reinfected from without, just as many are infected and reinfected by deep inhalation into the lungs.